## REMARKS

Claims 74 and 93 have been amended. Claims 74-93 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

### I. The Rejection of Claims 74-77, 80, 82-84, 86-88, and 91-93 under 35 U.S.C. § 103

Claims 74-77, 80, 82-84, 86-88, and 91-93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136, 1989) in view of Lereclus *et al.* (WO 94/25612). The Office Action states:

> At the time the invention was made, it would have been obvious to one of ordinary skill in the art to start with the DNA construct of Hung and place the "downstream region" and optionally, CryIIIa gene of Lereclus into said construct in order to successfully express either the mouse DHFG encoding gene or Bacillus thuringiensis CryIIIa gene in all Bacillus cells.
>
> One of ordinary skill in the art is motivated in inserting the "downstream region" of Lereclus into the DNA construct of Hung because such insertion results in mRNA protection thereby to more commercial scale expression of non-endogenous genes in a variety of Bacillus host cells, rendering the invention obvious.
>
> Finally, one of ordinary skill in the art has a reasonable expectation of success in inserting the "downstream region" and optionally, CryIIIa gene of Lereclus into the Bacillus cell and DNA construct of Hung because said downstream region already works successfully in Bacillus subtilis (see claim 40).

This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966).

Under 35 U.S.C. § 103, the law requires, when relying on a combination of prior art references to render a claimed invention obvious, that the prior art references contain within them a suggestion of the possibility of achieving the improvement of the claimed invention, such a suggestion being either express or implied. In re Sernaker, 217 USPQ 1 (Fed. Cir. 1983). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the

combination. Carella v. Starlight Archery, 231 USPQ 644 (Fed. Cir. 1986); In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). It is also impermissible to use the claims as a framework from which to pick and choose among individual references to recreate the claimed invention. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). A reference, or references, must show or suggest the properties and results of the claimed invention, or suggest the claimed combination as a solution to a given problem, in order to successfully be relied upon for an obviousness rejection. In re Wright, 6 USPQ2d 1959 (Fed. Cir. 1988). The mere fact that prior art references could be readily modified to form the claimed invention is not sufficient either, since the mere fact that the prior art could be modified would not make the modification obvious unless the prior art suggests the desirability of the modification. In re Laskowski, 10 USPQ2d 1397 (Fed. Cir. 1989). Applicant(s) believe the references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejections of the present claims.

Hung *et al.* teach a *Bacillus subtilis* cell comprising a DNA construct comprising a consensus *bla* promoter originated from *E. coli*, having the sequence TTGACA for the -35 region and TATAAT for the -10 region operably linked to a mouse dihydrofolate reductase (DHFG) encoding gene. Hung *et al.* do not teach or suggest a DNA construct further comprising an mRNA processing/stabilizing sequence.

Lereclus *et al.* teach an expression system comprising a CryIIIA gene, under the control of a *cryIIIA* promoter as well as a *cryIIIA* sequence called the "downstream region" or a "mRNA processing/stabilizing sequence", situated between the promoter and the coding sequence to be expressed and susceptible of acting at the post-transcriptional level during gene expression.

The Office suggests that it would have been obvious to one of ordinary skill in the art to start with the DNA construct of Hung and place the "downstream region" and optionally, *cryIIIA* gene of Lereclus into said construct in order to successfully express either the mouse dihydrofolate reductase encoding gene or *Bacillus thuringiensis cryIIIA* gene in all *Bacillus* cells. Applicant respectfully disagrees.

Lereclus *et al.* on page 9, lines 14-21, of WO 94/25612 (see U.S. Patent No. 6,140,104 for English translation) state:

> As to the nature of the promoter, it seems preferable to use a promoter derived from the host cell used for the expression of the gene of interest. However, in certain situations the use of an exogenous promoter may be indicated. For example, promoters such as the promoters of the degO, λPL, lacZ, cryI, cryIV or alpha-amylase genes may be used.

However, the results of Lereclus *et al.* do not show that placing the *cryIIIA* "downstream region" (also known as the *cryIIIA* "mRNA processing/stabilizing sequence")

downstream of a heterologous promoter has any positive effect. Lereclus *et al.* in Figure 4 of WO 94/25612 disclose the construction of pHT7901'lacZ where the *lacZ* promoter is situated upstream of the "downstream region" sequence which is upstream of the *lacZ* gene and pHT304'lacZ which is a control plasmid with only the *lacZ* promoter driving the *lacZ* gene with no "downstream region" included. However, on pages 33-34 and Figure 5 of WO 94/25612, the expression data from pHT901'lacZ and pHT304'lacZ demonstrate that placing the *cryIIIA* "downstream region" downstream of the *lacZ* promoter has no positive effect on expression of the *lacZ* gene. Lereclus *et al.* also disclose in Figures 4 and 6 of WO 94/25612 the construction of pHT7902'lacZ where the *cryIIIA* promoter is upstream of the *cryIIIA* "downstream region" which is upstream of the *lacZ* gene. The control is pHT907'lacZ (Figure 6) where the *cryIIIA* "downstream region" is absent. Figure 6 of WO 94/25612 shows that the pHT7902'lacZ construct increases expression of the *lacZ* gene relative to the pHT7907'lacZ construct. While Lereclus *et al.* show that the *cryIIIA* "downstream region" located downstream of the *cryIIIA* promoter has a positive effect on the expression of the *cryIIIA* gene and *lacZ* gene, there is no unequivocable evidence presented that the *cryIIIA* "downstream region" can be used with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene. In fact, based on the results of Lereclus *et al.*, the *cryIIIA* "downstream region" appears to be specific for the *cryIIIA* promoter.

Applicant submits that the references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejection of the present claims. Moreover, there is no motivation to inserting the "downstream region" of Lereclus *et al.* into the DNA construct of Hung *et al.* because there is no reasonable expectation of success of increasing expression of a gene based on the results obtained by Lereclus *et al.* wherein the mRNA processing/stabilizing sequence is foreign to the "consensus" promoter.

For the foregoing reasons, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

## II. The Rejection of Claims 89-90 under 35 U.S.C. § 103

Claims 89-90 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus *et al.* (WO 94/25612) further in view of Jorgensen *et al.* (WO 93/10249). The Office Action states:

> At the time the invention was made, it would have been obvious to one of ordinary skill in the art to start with the Bacillus host cell of Hung in view of Lereclus and use the instructions, genes (such as amylase or protease

encoding genes) and methods of Jorgensen in order to incorporate said construct into the chromosome of the Bacillus cell.

One of ordinary skill in the art is motivated in either using the intact DNA construct of Hung in view of Lereclus or using the construct of Hung in view of Lereclus further in view of Jorgensen wherein the reductase encoding gene of Hung is replaced by amylase or protease encoding genes of Jergenson, for chromosomal integration of a Bacillus host, according to Jorgenson. This is because integration of said DNA constructs into the chromosome of the host cell results in a more stable and long term transfection of the host, leading to a recombinant Bacillus host which can express the desired gene for many more generations, rendering the recombinantly expressed products more economical.

One of skill in the art has a reasonable expectation of success in integrating either of the above mentioned DNA constructs into the chromosome of Bacillus host cell according to Jorgenson because methods of chromosomal integration of genes in Bacillus and E. coli are well established in the prior art, as evidenced by the disclosure of Jorgensen, rendering the invention obvious.

This rejection is respectfully traversed.

Hung *et al.* and Lereclus *et al.* are discussed in Section II above.

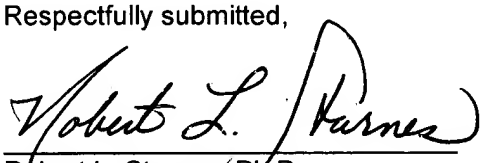
Jorgensen *et al.* disclose a *Bacillus* promoter derived from a variant of a *Bacillus licheniformis* alpha-amylase promoter for use in expressing heterologous genes.

For the reasons stated in Section II, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

## III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



Date: July 7, 2004

Robert L. Starnes, Ph.D.
Reg. No. 41,324
Novozymes Biotech, Inc.
1445 Drew Avenue
Davis, CA 95616-4880
530-757-8100
530-757-4715 (direct)